CALIFORNIA NEWBORN SCREENING PROGRAM REVIEW

February 25-26, 2005

National Newborn Screening and Genetics Resource Center
Austin, Texas USA
NNSGRC

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EXECUTIVE SUMMARY

California Newborn Screening Program Review
(February 25-26, 2005)

Background: At the invitation of the California Department of Health Services, a special newborn screening review team (Bradford L. Therrell Jr., Ph.D.; Marie Mann, M.D., MPH; W. Harry Hannon, Ph.D.) conducted a brief review of the California Newborn Screening Program (CNSP) on February 25-26, 2005. The team was sponsored by the National Newborn Screening and Genetics Resource Center (University of Texas Health Science Center at San Antonio) through a cooperative agreement with the Health Resource and Services Administration.

Overall Impression: The Review Team found the CNSP to be one of the strongest and more comprehensive programs in the country, particularly with respect to the ancillary services provided and overall program management. The infrastructure within the CNSP, while unique due to program size, population demographics, geography, and economics, appears to be working satisfactorily and is accomplishing its intended goal. The CNSP is one of the few programs with a physician serving as the program administrator, which provides added strength to program administration. The financing scheme and support services available within the program, including program evaluation, laboratory, follow-up, and education, are worthy examples for other programs. Dr. George Cunningham's medical knowledge and program leadership is particularly commendable. Additionally, the job performances and dedication of other program administrators contribute to the overall excellence of the program, including Dr. Fred Lorey, Dr. John Sherwin, Dea Harrel, and Kathleen Velazquez.

Few deficiencies exist, but a several areas were identified where further considerations to refine and improve the program may be useful

Concerns, Issues and Recommendations:

- **Advisory Committee:** An external advisory committee to the CNSP is not present and should be considered. California is one of only two programs not reporting the use of an advisory committee for external program input and support. The Review Team strongly supports the idea of a multi-disciplinary external advisory committee to provide input into program decision-making and to assist in external advocacy efforts.

Without participation from the community that provides program support (clinicians, hospitals, parents and families), the program faces a continuing uphill battle for community acceptance. Among representative stakeholders to be included in such an advisory group are parent advocates, pediatric subspecialists, general pediatricians, family practice physicians, hospital administrators, insurers, etc. GDB personnel should serve as liaison members or staff but should not hold voting positions.

A formal mission, regular meeting schedule and process for submitting input to the program should be established with wide dissemination of meeting minutes. Periodic program summary information should be reviewed and utilized for the basis of suggested program improvements.

Funding needed to support work of the Advisory Committee or its subcommittees should be included in fee considerations.

- **Business Practices:** The organization of the newborn screening business practices in California cannot easily be compared to those in any other state because of larger overall newborn population served in California. Only Texas serves a somewhat similar population in terms of size and demographics, but the program there is very different, having developed through the years in response to different political and economic pressures. The California program is the only one utilizing multiple screening laboratories and follow-up services through private sector contracts, and this system appears to be meeting the needs of the population served. Likewise, the financing scheme is different from other programs by virtue of hospital and Medi-Cal billing interactions (ie. the Medi-Cal system serves to virtually guarantee the payments will occur in a timely way). The Review Team was particularly impressed with the fact that the financing system assures that virtually 100% of billing fees will be reimbursed.

- **Multiple Screening Laboratories:** While there is little question about the efficiency and speed that results from decentralized follow-up in the CNSP, some questions exist relative to the cost efficiency of the decentralized laboratory testing program. It should be possible to improve the overall cost efficiency by decreasing the number of screening laboratories. For example, fewer tandem mass spectrometry (MS/MS) instruments and operators would be needed if the number of screening laboratories were decreased since each instrument is generally capable of analyzing approximately 100,000 specimens annually. Thus, a single centralized laboratory would require approximately 7-8 instruments (allowing for back-up) versus the almost double this number currently being prepared for operation. Two laboratories might require 4 instruments each. While, some laboratory redundancy is useful for insurance in case of a laboratory disaster, additional efforts to maintain equal services and quality across multiple laboratories is substantial and can be decreased by a decrease in the number of laboratories involved. The Review Team suggests that the issue of laboratory consolidation should be revisited.

- **Confirmatory Laboratory Testing:** The CNSP is one of only a few programs that has contractual arrangements with diagnostic laboratories to provide confirmatory laboratory testing.

  Explanation:
  There are four confirmatory laboratories that receive second dried-blood spot for confirmation of the abnormal results. These laboratories are:
  1. *Genetic Disease Laboratory for phenylketonuria and hypothyroidism*
  2. *Children Hospital of Los Angeles for galactosemia*
  3. *Children's Hospital of Los Angeles for biopterin*
  4. *Children's Hospital of Oakland for hemoglobinopathies.*

Incidental to this review, it was reported by at least one hospital that their hospital laboratory outsourcing does not allow repeat tests to be sent to the contracted laboratory. It is suggested that a study of hospital practices relative to use of the contracted laboratories might be informative, if these data do not already exist.

Additionally, it was noted that the referral strategy to contracted confirmatory laboratories was recently changed to a 'refer all' strategy. Most other screening programs request that some results may be resolved by a repeat screen (in cases where testing may not be extremely time critical) sent to the screening laboratory as a way of decreasing the number of confirmatory tests required. The Review Team suggests that the data be closely monitored to determine if the 'refer all' strategy currently employed is cost efficient, since the numbers being referred may be significantly higher than with the previous policy. This may be particularly important as new conditions are added to the program and more presumptive positive results are reported.

- **Screening Laboratory Contract**: It doubtful that cost differences between California model of public/private partnership and a single source contract for private laboratory testing would be significant. A detailed cost accounting of the CNSP and private sources would be required in order to answer this question in depth. The Review Team notes that care must be taken to compare likes to likes such that laboratory services are compared to laboratory services and follow-up/education services compared to follow-up/education services. It is sometimes the case that laboratory services from a private source are compared to comprehensive screening services that include laboratory, follow-up/education, and other ancillary services. In this way, the laboratory services appear to be less costly since they are not being compared to laboratory services alone. The cost of laboratory testing alone is less that 50% of the total program cost in some screening programs.

- **Communications/Education:** The use of local follow-up/educational personnel provides more comprehensive educational services than are present in most other screening programs. Likewise the attention to birthing facility visits for training and public relations is commendable.

In addition to current information available on the Genetic Disease Branch website, future materials might include disease-specific newsletters, annual reports, advisory committee meeting announcements and minutes, and more extensive disease-specific educational material and linkages. Dedicated space for different screening conditions or groups of conditions may offer an opportunity to obtain more parent interest and may provide increased educational opportunity.

The lack of availability of previous newsletters indicated that there was no real schedule as to when program newsletter might be published. The last newsletter accessible on the website was published in 2003. Comprehensive summation reports of program data were also not readily available. Articles published by the program personnel describing research and program activities were also not available either through linkages or in downloadable format.

- **Documentation/Data:** The computerized tracking system currently being implemented should be carefully reviewed to ensure that it meets all relative record keeping requirements. The CNSP served as a beta test site for evaluation of the National Newborn Screening Information System (NNSIS) recently implemented as a source of program evaluation data. The

program is encouraged to develop routine input into the system so that the data set can be kept current. Consideration should be given to electronically downloading information after the new California computer system is stabilized.

- **Quality Assurance:** The quality assurance of the laboratory testing portion of the CNSP is well-established and appears to be working smoothly and efficiently. Less clear is the extent of quality assurance for the remainder of the CNSP. If not currently established, periodic audits of the activities of the Area Service Centers should be undertaken in order to evaluate and ensure the quality of the follow-up/education process. A periodic systems' analysis should be performed to identify any gaps in the overall screening system.

The Review Team suggests that the practice of assessing the quality of filter paper collection devices should be reviewed and consideration given to its discontinuation if other activities now in place (FDA, CLSI/NCCLS, CDC) provide sufficient quality assurance to satisfy CNSP needs. The California NSP is the only program continuing to engage in this activity.

The current laboratory practice of a single analysis and release of results for follow-up confirmatory testing without a retest protocol varies from the standard of practice in all other screening laboratories with which the review team is familiar, and should be reconsidered. That is, current laboratory protocols do not require a check of reproducibility of the results of individual sample analyses, particularly as they relate to results considered outside of the expected range. All other screening laboratories perform a reaccession and recheck of specimen results for those specimens with initial results outside of the expected range. Indications from contract laboratory personnel indicated occasional unexplained reproducibility problems when a confirmatory result was compared to the original screening result. Occasional discrepancies that could not be resolved through Genetic Disease Laboratory investigations appeared to be written off as "fliers" that sporadically and spontaneously resulted from unexplained technical issues likely caused by instrumental anomalies. Because it is possible that these unexplained differences between screening and confirmation may have resulted from punching or other clerical errors, including hospital errors in patient identification, it is recommended that the laboratory testing protocol include a reaccession, reanalysis, and result revalidation step prior to release of out-of-range screening test results.

- **Consolidation of Newborn Screening Programs:** Many state newborn screening programs have developed consolidated hearing and blood spot screening as a more efficient way of providing patient services. The Review Team strongly encourages continued consideration of the possibilities of consolidated data management and program integration between newborn hearing screening and the dried blood spot newborn screening program.

- **Integrated Health Information Systems:** Some newborn screening programs have realized that information obtained from dried-blood spot screening can become an integral part of integrated health information systems. Other useful data might include immunization status, newborn hearing screening status, CSHCN Program, WIC Program, and various other California DHS program-related information. Additionally, in order to ensure full population coverage in newborn screening and to validate demographic data, integration with birth certificates is desirable. A number of states are now developing integrated information systems. These

systems contain a central repository of certain data elements that are consistent among different programs, such as the basic patient demographic information – name, date of birth, sex, race/ethnicity, etc. and allow data sharing with other program-specific data systems.

- **Long Term Tracking and Outcome Evaluation**: It appears that long-term tracking and outcome evaluation are areas of need in California, and areas that could be emphasized as program expansion occurs. In order to provide critical outcome data for program evaluation, consider an annual review of patients' compliance with medical management protocols and patients' health/development status. Long-term outcome measures and indicators should be specific for each condition. Consider publication of a comprehensive annual report that includes summary data from screening and outcome monitoring.

- **Education of Policy Makers:** It is essential for the CNSP to continue to be proactive in addressing the newborn screening educational needs of California legislators. Also, it is important for the California DHS to make sure that program and other scientific information needed for sound policy decisions are available to the policy makers.

CONSULTATION REPORT
CALIFORNIA NEWBORN SCREENING PROGRAM

1.0.0 Introduction

On February 25-26, 2005, a specially formed Newborn Screening and Genetics Review Team (brief resumes in Appendix 1), including representatives of the National Newborn Screening and Genetics Resource Center (NNSGRC), the Genetic Services Branch, Maternal and Child Health Bureau (MCHB), Health Resources and Services Administration (HRSA), and the Newborn Screening Branch, Environmental Health Center, Centers for Disease Control and Prevention (CDC) briefly reviewed the California Newborn Screening Program (CNSP). This review was at the invitation of Catherine Camacho, Deputy Director, Primary Care and Family Health Division, California Department of Health Services (CDHS). In addition to meeting with Ms. Camacho, and other CDHS staff members associated with the California Newborn Screening Program (CNSP), the Review Team also visited with medical staff at the Kaiser Oakland Genetics Department, Oakland, and the Kaiser Hospital Laboratory, Berkeley. An exit meeting was held with CDHS staff on February 26 at which time a preliminary version of this report was given orally and a general program discussion was held.

The initial meeting of team members and local health department staff was held on February 25 at the Richmond CDHS offices. This meeting included, in addition to the team members and Ms. Camacho, Beth Fife (Assistant Deputy Director, Primary Care and Family Health Division), Susann Steinberg, M.D. (Chief, Maternal, Child and Adolescent Health Branch) - by telephone, Les Newman (Assistant Branch Chief, Maternal, Child and Adolescent Health Branch), John Sherwin, Ph.D. (Chief, Genetic Disease Laboratory Section), Fred Lorey, Ph.D. (Chief, Program Development and Evaluation Section), Dea Harrel (Chief, Information Technology and Services Section) and Kathleen Velazquez (Chief, Newborn Screening Section). Following an initial welcome by Mr. Newman and comments regarding the purpose of the visit and specific concerns from Ms. Camacho, an in depth program overview was presented by Ms. Velazquez (program administration/education/follow-up), Mr. Newman (budget) and Dr. Sherwin (laboratory services). Information from these presentations and from the CNSP website is included in the Program Overview section that follows.

In the afternoon of the first day, the Team visited within the Richmond facility for a demonstration of the data system by Ms. Harrel, discussions about clinical services, and a brief tour of the Genetic Disease Laboratory (GDL). This was followed by a visit to the Permanente Medical Group, Inc., Regional Laboratory, Berkeley, where the Review Team met with the pertinent staff members there to discuss interactions and shared activities with the CNSP. In addition to team members and Dr. Sherwin, hospital staff members present at this meeting included: Gwen Wong (laboratory supervisor), Mary Gabel (perinatal nurse), Roberta Cunningham, M.D. (physician liaison), and Pam Midldleton (neonatal intensive care manager). The following morning, the team visited the Kaiser Genetics Department in Oakland. Participants in this meeting included Kathleen Velazquez (CDHS), Heidi Lerner (CDHS nurse coordinator), John Baker, M.D. (metabolic specialist), Elaine Eastman (nurse follow-up coordinator) and Jennifer O'Keefe (nurse follow-up coordinator).

The review team was impressed with the cooperation of all personnel with whom it interacted, both at the CDHS and at the other facilities. The program staffs at the CDHS and at the hospitals appear dedicated and interested in maintaining a successful, effective newborn screening program as evidenced by their involvement and cooperation in this review. This cooperative effort has allowed the CNSP to successfully and efficiently carry out its mission of detecting newborns with congenital conditions and ensuring that the services they receive are timely and effective, and ultimately result in significant reductions in morbidity and mortality.

1.1.0 Program Overview

The following overview of newborn screening and the current public health situation in Maine was prepared from written information shared with the Review Team, website information, and information presented at meetings with program and hospital staff.

Newborn Screening began in California in 1966 with testing for phenylketonuria (PKU). In October 1980, the program was expanded to include galactosemia (GAL), primary congenital hypothyroidism (CH), and a more comprehensive follow-up system. In 1990, screening for sickle cell disease was added to the program and allowed for the identification of some of the related non-sickling hemoglobin conditions, including beta^0 thalassemia major, and Hb E-Beta Thalassemia. In 1999, the Program implemented screening for hemoglobin H and hemoglobin H - Constant Spring disease. Following a pilot project to determine that feasibility and appropriate mechanisms for expanded metabolic screening using tandem mass spectrometry (MS/MS), program expansion to include comprehensive reporting of the metabolic conditions detectable with MS/MS and congenital adrenal hyperplasia (CAH) is expected to begin by August 1, 2005. Further expansion to include biotinidase deficiency (BIO) and cystic fibrosis (CF) is anticipated in 2006.

State regulations (17 CCR 6500) require that prenatal care providers give pregnant women informational material about the newborn screening program. Because some women do not receive prenatal care, the same informational material, *Important Information for Parents about the Newborn Screening Test*, is also distributed upon admission to a licensed perinatal health facility for delivery. Additionally, county birth registrars are required to notify persons registering the birth of a baby born outside of licensed perinatal health facilities of newborn screening within 30 days of the birth. The birth registrar must provide the person registering the birth with the same pamphlet and information about how to have the baby tested. The registrars are also required to notify the NBS Program of these births and must complete and send the NBS-OH form (*Notification of Registration of Birth Which Occurred Out of a Licensed Health Facility*) to GDB. The CNSP supplies copies of the pamphlet, *Important Information for Parents about the Newborn Screening Test,* at no cost to all health professionals who serve maternity patients, to hospitals that provide maternity and/or newborn care, to local health departments, and county birth registrars.

Program expansion is an ongoing consideration and includes evaluation of conditions based on the following criteria:

- Important health problem in terms of frequency, seriousness, and high costs of care
- Associated with disease/known symptoms
- Effective treatment exists that improves quality of life
- Easy to detect, reliably and economically
- Adequate methods of confirmation and follow-up

Other considerations, including the number of babies screened daily, may affect whether and/or when disorders are added to the screening program.

Newborn screening is a responsibility of the Genetic Disease Branch (GDB) of the CDHS. The mission of the GDB is "To serve the people of California by reducing the emotional and financial burden of disability and death caused by genetic and congenital disorders." The following tasks support this mission:

- Screening newborns and pregnant women for genetic and congenital conditions through screening programs that provide testing, follow-up and early diagnosis to prevent adverse outcomes or minimize the clinical effects.
- Ensuring quality of analytical test results and program services by developing standards and quality assurance procedures, and monitoring their compliance.
- Fostering informed program participation in an ethical manner through patient, professional, and public education, and accurate and up-to-date information and counseling.
- Providing ongoing critical review, testing, and evaluation of existing programs to ensure that program objectives and goals are being met.
- Developing programs to adopt new methods and implement new services to enhance the effectiveness and efficiency of current and future prevention programs.
- Promoting the use of high-quality consumer education materials.

In 1989 the Maternal PKU Project became the Maternal PKU Program, a permanent part of the GDB. The goals of the program are:

- To identify and locate young women of childbearing age with PKU;
- To inform such women of risks and options for preventing/minimizing poor pregnancy outcomes;
- To inform health professionals of the need for identifying and appropriately managing such pregnancies;
- To maintain a permanent tracking system of all present and future women with PKU of childbearing age.

A continually updated registry of all potential childbearing women with PKU in the state of California was also established. All of the information provided to and contained in the MPKU Registry is confidential. A maternal PKU camp/conference was developed in order to achieve the educational goals for young women with PKU.

The Genetic Disease Branch, through the Genetic Disease Laboratory, offers phenylalanine blood level monitoring to all individuals with PKU seen at California Children's

Services (CCS) -approved metabolic centers throughout California at no cost to the patient. This program has facilitated getting results and increased access to testing for patients. Beginning in July 2003, parents of newborns identified with Hb S-trait, Hb C-trait, and Hb-D trait may receive telephone information from the CNSP through a toll free number. A sickle cell counselor also provides information about family testing that is available as a program service at no charge.

In addition to an active educational part of the newborn screening website (http://www.dhs.ca.gov/pcfh/GDB/html/NBS/EducationMaterial.htm), other educational resources are provided through GeneHELP, a resource center housed and maintained by the GDB to assist health care practitioners, other professionals and the general public in the selection, utilization, and development of accurate and appropriate educational materials on genetic screening, genetic disorders and services. The resource center contains information on a variety of different formats which include ½" VHS videotapes, pamphlets, brochures, booklets, curricula, and slides. GeneHELP searches for new genetic health education materials on an ongoing basis from many different organizations. New materials are reviewed using a staff of consumers, teachers, health educators, doctors, genetic counselors, and nurses. GDB staff and advisory committees of professionals and consumers review materials and make recommendations on materials based upon many criteria including:

- Clarity of message
- Reading level
- Readability
- Cultural diversity/sensitivity
- Print size
- Graphics
- Content accuracy
- Relevancy
- Presentation

All educational materials are categorized as either recommended or not recommended. In addition, all sickle cell materials are also categorized as either approved or not approved for use by State-approved sickle cell education and counseling programs. All comments and information on the evaluated materials are then entered into and maintained in the GeneHELP Database. Currently there are nearly 800 titles of materials on certain genetic diseases, hemoglobinopathies, birth defects, and newborn screening and prenatal diagnosis issues. Requestors can obtain a computer printout of recommendations for use of the materials, plus the cost and how to obtain them. In addition, informational searches and referrals to other agencies and resources can be obtained. Sample copies and small quantities of many of the items are available free of charge to California health professionals.

The California statutes and regulations limit the number of newborn and prenatal screening laboratories because the quality of testing for low incidence conditions requires a certain minimum volume of testing for optimal performance. Currently testing is carried out at six area laboratories located throughout the state and at two laboratories that each serve a comprehensive prepaid group practice in excess of 20,000 births per year. The Genetic Disease Laboratory (GDL) in Richmond also maintains capability to serve as a back-up laboratory in case of emergency. In addition to the eight screening laboratories, there are also contracts with three confirmatory laboratories. The average test volume processed daily at the screening laboratories ranges from 80 to 300 dried-blood-spot specimens from newborns and 70 to 230 maternal serum specimens for prenatal screening.

In addition to the GDL, the currently contracted Newborn and Prenatal Screening Laboratories (NAPS) include:

- Western Clinical Laboratory, Inc.; Roseville
- The Permanente Medical Group, Inc., Regional Laboratory; Berkeley
- Allied Laboratories, Inc.; Cupertino
- Fresno Community Hospital Laboratory; Fresno
- Quest Laboratory; Van Nuys
- Memorial Medical Center of Long Beach; Long Beach
- Southern California Permanente Regional Endocrinology Laboratory; Carson
- Orange Coast Health Tech Regional Laboratory; Fountain Valley

The confirmatory laboratories include:

- GDL (phenylketonuria and hypothyroidism - second dried-blood-spot)
- Children's Hospital of Los Angeles (galactosemia confirmatory testing)
- Children's Hospital of Los Angeles (biopterin testing)
- Children's Hospital of Oakland (hemoglobin reference laboratory)

Private laboratories compete for the use of identical equipment obtained through a master reagent-instrument agreement. Should a contract laboratory fail to provide the appropriate testing, the equipment is available for use by another laboratory. The GDL prescribes standardized protocols for the contract laboratories including test methods, sample collection, quality control, and result reporting. The GDL specifies the calibrators to be used and defines the dose-response relationship. Training is provided to the testing personnel at the contract laboratories and, in collaboration with the Genetic Disease Branch, cutoff rules are developed for identifying results that are outside of the expected range of results. The cutoff rules are identical for all testing sites. Test results from the contract laboratories are electronically transmitted to GDL daily and quality control officers at GDL review the results for accuracy before the results are released to physicians.

The strong centralized control by GDL is intended to assure uninterrupted and uniform screening. GDL monitors potential problems that, without intervention, could lead to a delay in the reporting of results, and maintains inventories that can be used to supply laboratories in the event of unforeseen shortages. GDL manages the reassignment of supplies and equipment between laboratories when needed to meet urgent demands. The screening laboratory contracts specify:

- Financial payments
- Test methodology
- Turnaround time
- Equipment
- Calibrators and controls
- Accession of specimens
- Methods for reporting results
- Back-up arrangements
- Proficiency testing
- Equipment maintenance
- Record keeping
- Record keeping
- Source of specimens
- Actions for inadequate specimens, presumptive positives and repeat specimens
- Space allocation
- Job titles
- Overload capacity, the ability to absorb the workload of another

- Specimen handling and storage contract laboratory if needed

Matters under direct control of each contract laboratory include:

- Personnel – hiring, salaries, assignments, training, scheduling, supervision, evaluation, continuing education, licensure or certification
- Facilities – layout, environmental quality, maintenance
- Supplies – water, consumables (but not equipment, specified reagents, calibrators, controls)
- Standard laboratory practices – safety and health, general procedures
- Specimen transport – mail or courier.

For test results for PKU, GAL and CH indicating increased risk of a condition, the NAPS laboratory immediately reports to an assigned Area Service Center (ASC). These coordinators are located throughout the state in the seven regional offices listed below and are linked to the NBS Program central computer in Richmond:

- Kaiser Permanente – Northern California
- Kaiser Permanente – Southern California
- Stanford Medical Center
- Children's Hospital Central California
- UCLA Medical Center
- Harbor/UCLA Medical Center
- UC San Diego

For results outside of the expected testing limits, a second blood sample (recall specimen) is requested. The recall specimens for PKU and CH (borderline values only) are sent to the GDL for testing. Recall specimens for galactosemia are sent to the State-funded GAL confirmatory laboratory at Children's Hospital Los Angeles. The primary care practitioner is responsible for notifying the family about the test results and for obtaining a recall specimen. The physician may request assistance from the ASC newborn screening coordinator. Parents are also notified of the initial positive test result by letter from the ASC Coordinator. Enclosed with the letter is a pamphlet that explains the meaning of an initial positive screening result and the need for recall testing. A copy of the letter and the pamphlet are also sent to the newborn's physician. The Coordinator tracks all initial positive cases to ensure that appropriate follow-up occurs.

In the case of hemoglobinopathy tests, the GDL reviews and releases the hemoglobin results. Potentially clinically significant hemoglobinopathies and other initial positive results are reported on a daily "Interesting Case Report" to the ASCs. An ASC NBS Coordinator from the respective Center immediately telephones the newborn's physician to provide interpretation of the test and explain necessary follow-up. Hemoglobin results requiring additional confirmatory testing are sent to the hemoglobin reference laboratory at Children's Hospital Oakland.

When recall test results indicate the need for further action, the diagnostic laboratory informs the ASC. The ASC newborn screening coordinator in turn notifies the newborn's physician of the recall test results. For confirmed positive results, the Coordinator will provide information on the confirmatory test and explain the recommended follow-up. Medical

consultants are available at each ASC to provide additional information and consultation when necessary. Coordinators can also assist the provider in referring a family to a CCS-approved Metabolic, Endocrine or Sickle Cell Disease Center for specialized diagnosis and treatment. All infants with non-negative results are tracked to ensure confirmation of diagnosis and initiation of treatment. However, according to information available on the CNSP website, approximately 1,000 babies (0.5% of the births) are not screened at birth, another 125 with inadequate results of the initial test never receive a second test. Likewise, a 'very small number' of newborns with initial positive test results are lost to follow-up. The CNSP actively attempts to education primary care practitioners of their role in ensuring that all California newborns receive newborn screening.

The ASC also has the responsibility of following up on all newborns on whom an inadequate newborn screening specimen was collected. The NAPS laboratory calls the appropriate ASC when the sample is inadequate. The ASC, in turn, calls the newborn's physician (or the hospital neonatal intensive care unit, if the infant is still hospitalized) to arrange for a repeat specimen. A follow-up letter is sent to the physician and a Confirmation of Contact (C of C) is data-entered into the State computer. The health facility where the initial specimen was obtained (or another facility more convenient to the family) is notified about the returning newborn and the repeat test that is needed. The ASC Newborn Screening Coordinator will follow a case until it is resolved.

In order to continually assess screening test performance ant the success of the program in meeting its goals, the Program Development and Evaluation Section is responsible for data gathering and information on program improvements, including new test availability. Staff members conduct ongoing daily monitoring to assess screening test performance to assure that services are provided in a timely and effective manner. To aid in evaluating completeness and effectiveness of the CNSP, the California Code of Regulations (Title 17) requires that all physicians diagnosing a preventable heritable disorder, for which testing is required, report a diagnosis to CDHS. If this process identifies a missed case, the case will be investigated to determine if changes in policies or procedures are necessary to ensure that a miss for similar reasons does not reoccur.

Long-term follow-up of program data allows staff to track the health impact of screening services, including the study of important trends in the use of services among specific populations and regions throughout the State. Research studies are developed to answer questions about factors associated with birth defects and genetic disorders, including, for example, genetic mutations within the California population admixture associated with newborn screening condition such as CF. Disease surveillance is another Section responsibility that occurs partially through registries of diagnosed disorders and can be used to determine how well the screening program identifies the targeted screening conditions (detection rate). Registries of affected cases make it possible to better understand characteristics of individuals that are detected through the screening process and provide data identifying epidemiologic studies that might lead to improvements in the quality of the screening program.

Table 1 below gives some of the case detection data reported to the National Newborn Screening and Genetics Resource Center (NNSGRC) and to the Council of Regional Networks

for Genetic Services (CORN) over the past decade. National data are now being entered into an online data system, of which the CNSP served as a beta testing facility and is now an active data contributor.

Table 1. California Newborn Screening Summation 1991-2000 -Taken from National Newborn Screening Reports of Maine Newborn Screening Program Data and validated by the Program Coordinator.

Year	Births[1]	PKU	CH	GAL	Hb FS	Hb FSC	Hb FSA	Hb FAS
1991	610,385	26	218	9	76	32	13	4,949
1992	602,035	29	211	6	72	45	6	4,903
1993	585,564	13	210	6	83	33	14	5,095
1994	568,153	16	197	6	72	39	9	4,921
1995	552,322	14	192	8	66	33	13	4,607
1996	539,661	20	185	12	57	29	9	4,154
1997	524,865	11	195	8	65	34	9	4,218
1998	522,290	13	200	7	78	21	6	4,325
1999	519,102	15	236	5	69	26	4	4,315
2000	532,500	18	254	5	53	28	10	4,279
Totals	5,556,877	175	2,098	72	691	320	93	45,766
Incidence (1 case per …)		31,754	2,649	77,179	8,042	17,365	59,751	121

[1] From National Center from Health Statistics. Hb = Hemoglobin

Currently, the newborn screening fee is $78.00 for support of the comprehensive screening program services previously described. Residual specimens remaining after analysis are stored indefinitely, desiccated at –20 degrees C.

1.3.0 Organization of Consultation Report

This Consultation Report is organized to first address items identified by the California Department of Health as issues of interest (see Appendix 2). Comments on these issues are followed by a discussion of other points considered important by the review team. Finally, a summation is given using a template in which strengths, weaknesses and possible future actions are enumerated. It is suggested that the possible actions be reviewed and developed into an action plan for strengthening the program. Persons reviewing this report are referred to Appendix 3 for published guidelines considered essential to the success of newborn screening systems. These guidelines, entitled *U.S. Newborn Screening System Guidelines: statement of the Council of Regional Networks for Genetic Services (CORN)*, were the result of findings from multiple state consultations similar to the one conducted in California, and even though they were first published in 1992, they have withstood the test of time as reasonable and comprehensive general guidance. All members of the team are available for further consultation either collectively or independently if needed.

2.0.0 Issues from the Program

The issues in this section were submitted to the Review Team from Ms. Camacho prior to the visit, and they will be given priority as a major focus of the review. Additionally, the team identified some issues for comment, and these are included in the section that follows.

2.1.0 Business Practice

Currently in the United States, there are two primary mechanisms for funding newborn screening programs - fees and legislative appropriations. Programs also receive funding either directly (direct funding transfers) or indirectly (service delivery) from other sources such as Title XIX (Medicaid), Title V [Maternal and Child Health Block Grant, including Children with Special Health Care Needs program (CSHCN)], Women Infants and Children's (WIC) program, and various other programs (including state appropriations). Further elaboration on current financing strategies can be found in the 2003 Report of the Government Accounting Office available online (http://www.gao.gov/new.items/d03449.pdf).

Historically, newborn screening programs have relied heavily on tax revenues and the public health laboratory for the testing services considered essential to newborn screening. Over time, programs have expanded from a single screening condition, PKU to more conditions. These expansions were motivated in the 1970s and 1980s by the ability to screen for higher prevalence conditions such as CH. With expanded screening came increasing demands for related program services, screening for more conditions, and consequently the need for additional funding. State legislatures gradually shifted from tax revenue based financing to fees. Table 2 gives a comparative summation of the current financing schemes of the 51 U.S. newborn screening programs (50 states and the District of Columbia). Of the 51 programs, all but 5 currently obtain at least some of their funding through a fee process.

The CNSP has supported itself through a fee process for many years, and was one of the first programs to include comprehensive screening services in its fee. Notably, program services beyond laboratory testing such as follow-up of abnormal and unsatisfactory testing results (with primary care physicians, subspecialists, parents, and others who might be associated with patient care), education of parents and healthcare professionals, treatment/medical management, and long-term outcome monitoring are included in the financing plan. Compared to most other programs in the country, the CNSP business and financing plan is an example of thoughtful and careful considerations, and serves as a model of how a newborn screening fee should be structured. Additionally, the mechanism of fee collection appears to work well and is one of the most successful in the country.

Table 2. Tabulation of State Newborn Screening Program Fees

State	Births (Occurrence) In 2001	Percent Medicaid births (2000[a])	Number of screens required	Number of disorders currently mandated (1/2005)	Current Fee 1/2005	Notes
Alabama	59,766	45.0	1	14	$139.33	Two screens strongly recommended.
Alaska	9,907	52.0	1	>30	$55.00	Fee includes any repeats.
Arizona	85,757	44.0	2	8	$20.00	Separate fee for each mandated specimen.
Arkansas	36,301	43.7	1	4	$14.83	
California	528,539	42.4	1	>30	$78.00	
Colorado	67,100	32[b]	2	7	$53.25	Fee includes 2 mandated specimens (2-part form).
Connecticut	43,179	26.7	1	>30	$28.00	
Delaware	11,360	41.0	2	29	$64.00	Fee includes 2 mandated specimens and any repeats.
District of Columbia	15,037	28[b]	1	7	No Fee	
Florida	205,991	44.0	1	5	$15.00	
Georgia	134,402	44.0	1	10	No Fee	
Hawaii	17,127	25.0	1	>30	$47.00	
Idaho	20,161	34.2	1	>30	$23.00	$46 for double kits if screening occurs prior to 48 hrs.
Illinois	181,086	37.2	1	>30	$47.00	
Indiana	86,710	42.0	1	>30	$62.50	Includes $32.50 laboratory surcharge and all repeats.
Iowa	37,756	23.0	1	>30	$56.00	Fee includes any repeats.
Kansas	39,052	12[b]	1	4	No Fee	
Kentucky	53,227	38.8	1	4	$14.50	
Louisiana	65,620	41.0	1	5	$18.00	Fee expected to increase to $40.00 later in 2005.
Maine	13,567	20[b]	1	9	$44.00	
Maryland	68,663	29.0	1	>30	$42.50	Fee includes repeats; 2 screens strongly recommended.
Massachusetts	82,237	24.2	1	10	$54.75	
Michigan	132,159	27.7	1	11	$55.72	Fee includes any repeats.
Minnesota	67,428	31.3	1	>30	$61.00	
Mississippi	41,145	53.7	1	40	$70.00	
Missouri	76,690	39.0	1	14	$25.00	
Montana	10,935	40.0	1	4	$39.34	
Nebraska	25,107	28.8	1	6	$30.75	
Nevada	31,007	27.6	2	>30	$60.00	Fee includes 2 mandated specimens (2-part form).
New Hampshire	14,055	20.8	1	6	$18.00	Fee includes hemoglobinopathies when requested.
New Jersey	112,639	23[b]	1	20	$71.00	
New Mexico	26,808	49.6	2	6	$32.00	Fee includes 2 mandated specimens (2-part form).
New York	255,029	41.1	1	>30	No Fee	
North Carolina	119,132	40.5	1	26	$10.00	
North Dakota	8,839	28.0	1	29	$36.00	
Ohio	152,033	33.1	1	30	$33.75	
Oklahoma	48,895	46.0	1	7	$75.59	Fee includes hearing screening.
Oregon	46,200	32.2	2	26	$54.00	Fee includes 2 mandated specimens (2 -part form). Extra single forms are $27.
Pennsylvania	143,957	25.0	1	6	No Fee	Many hospitals offer extra tests for fee. Fees vary.
Rhode Island	13,319	35.4	1	9	$59.00	
South Carolina	53,255	47.0	1	30	$42.00	
South Dakota	10,784	32.8	1	3	$18.53	Fee does not include hemoglobinopathies if requested.
Tennessee	83,521	37.7	1	>30	$47.50	
Texas	370,482	45.1	2	5	$19.50	Separate fee for each mandated specimen.
Utah	49,041	25.8	2	4	$31.00	Fee includes 2 mandated specimens (2-part form).
Vermont	6,149	23.0	1	21	$33.30	
Virginia	96,535	22.7	1	9	$32.00	
Washington	79,078	42.5	1	9	$60.90	Fee includes repeats; 2 screens strongly recommended.
West Virginia	21,000	55.2	1	4	No Fee	
Wisconsin	68,006	35.5	1	26	$65.50	$30.00 laboratory surcharge included in fee.
Wyoming	5,758	38.0	1	7	$45.00	Fee implemented for first time August 1, 2004.
TOTAL	4,031,531	39[b] (Nationally)				

(a) From Kaiser State Health Facts Online, http://www.statehealthfacts.kff.org.
(b) 2000 Medicaid statistics unavailable so statistics are taken from Kaiser Commission on Medicaid and the Uninsured, 1995.

Additional fee increases can be anticipated as the program improves and expands its services. It is important to have a sound accounting basis on which to calculate the fee and as currently appears to be the case, the fee should cover all program expenses including education, follow-up, linkages to services, counseling, and other activities associated with the program including limited treatment/medical management where possible (see report from the American Academy of Pediatrics Newborn Screening Task Force - *Pediatrics* 2000;106:383-427). In maintaining a fee, it is important to have the support of the majority of those who might be affected including the physicians, hospitals, insurers, Medicaid administrators and others. In cases where an active advisory committee is functioning, this committee can serve as the venue for community input problem solving and advocacy. The use of an external advisory committee is not practiced in California and should be considered. The advisory committee and other stakeholders should be involved in financial and other decision-making processes so that the community can feel a sense of ownership of the program and its decisions. It is important for the public and others involved in financing newborn screening to understand that newborn screening is a system and system finances MUST ultimately be comprehensive if newborn screening is to be effective. Failure to adequately consider overall system finances and services ultimately results in lower quality of the screening program.

In cases where program expansion requires significant increases in operating expenses, such as with expanded MS/MS screening, start-up costs can be (and usually are) significant due to the cost of new equipment, space and personnel considerations, and public/professional education. As in California, other programs have found it necessary to increase the income from fee revenue in advance of providing the actual testing program because of start-up costs (sometimes called research and development). In cost comparisons, it is important to realize that the costs outside of laboratory testing are often equivalent to or higher than these costs depending on the ancillary services required. A recent increase of $18 in California to offset the anticipated program expansion is reasonable when viewed in this light.

2.1.1 Organization, administration and infrastructure of the California NBS program.

The CNSP appears to be a successful preventive public health program that has served the newborn screening needs of California newborns for over 30 years. With over 570,000 births annually, California ranks number 1 in the number of births in the country, and as such, is faced with many more challenges than most programs in providing quality health care services. Except for Texas, the number of newborns screened in California is more than double any other program. The number of specimens tested is less than the Texas program because each of the 370,000 newborns in Texas must receive two tests, but the extremely high volume of specimens in both states makes the challenges in service delivery similar. Because of the larger overall population of newborns served in California, the organization of the newborn screening business practices in

California cannot easily be compared to those in any other jurisdiction, including Texas.

The administration and infrastructure of the CNSP appears to provide a quality newborn screening program for the citizens of California. The use of contracted laboratories and follow-up service centers, public or private, to provide public services, is a successful example of partnership building that can serve as an example to other programs. Initially faced with opposition from private sector laboratories when a public health laboratory model was considered in developing the newborn screening infrastructure (a model common in many other states), the alternative contractual organization of multiple private laboratories under the strict oversight of the public health laboratory has proven to be effective. Its success is likely due to thoughtful planning and the manner in which laboratory quality is assured, since somewhat similar models using multiple laboratories in other states generally have not been successful.

Newborn screening laboratory procedures are chosen to provide maximum sensitivity and specificity in a screening environment. Ideally, a low number of patients will be recalled for further testing based on analytical cutoff values selected so that, if possible, no patients with a condition of interest will be missed. Because analytical procedures for testing dried blood spots must be extremely sensitive because of the low volume of blood or serum tested, it is often difficult to obtain identical quality from different screening laboratories. The variables that affect analytical results are considerable and are often magnified when the instrumentation used in an analysis is complex. External proficiency checks provide the best means of ensuring that testing quality is maintained. In a system such as the multi-lab model in California, this means that very close external oversight must exist. Given the performance of the California program in the national proficiency testing program provided by the Centers for Disease Control and Prevention (CDC), quality laboratory testing appears to be in place. Thus it follows, that the internal methods currently in use in the program (Section 1.1.0) to assure satisfactory external proficiency testing performance are working.

There are currently 8 contracted laboratories, most with a volume of testing in excess of 50,000 specimens. Other screening programs have shown that the best quality and efficiency can be obtained in laboratories testing at least 50,000 specimens. Several other newborn screening programs routinely analyze in excess of 100,000 specimens annually, with New York routinely analyzing approximately 300,000 specimens and Texas analyzing over 700,000 specimens (although Texas does not yet test using MS/MS). Thus, while there are good reasons to have multiple screening laboratories within the State for back-up and because more testing generally requires additional laboratory space, it should be possible to improve the overall cost efficiency by decreasing somewhat the number of screening laboratories. For example, fewer MS/MS instruments and operators would be needed if the number of screening laboratories were decreased since each instrument is generally capable of analyzing approximately 100,000

specimens annually. Thus a single laboratory would require approximately 7-8 instruments (allowing for back-up) versus the almost double this number currently being prepared for operation. Two laboratories might require 4 instruments each. The final number rests in the confidence of the oversight program in ensuring that sufficient back-up capability exists and whether space requirements can be met. The Review Team suggests that the issue of laboratory consolidation be revisited with the idea of consolidating laboratory services where possible so that at least 50,000 specimens (preferably 100,000 for improved cost efficiency) are routinely analyzed in all laboratories. Additionally, where laboratories are located close geographically, consideration should be given to consolidation and more efficient geographic distribution.

Follow-up services are routinely provided in ASCs distributed geographically around the State as outlined in Section 1.1.0. Within the seven centers are approximately 25 FTEs. This follow-up system appears to efficiently and effectively meet the needs of the CNSP. With the installation of the new data management system, records will be electronically maintained and the capability exists for extended medical records that can provide a data capture system for long-term follow-up. While the CNSP has extensive support from subspecialists who act as program consultants, there is no formal advisory committee to provide needed community input to the program. Many programs draw on such committees for advice and advocacy when program refinements are needed. In contrast, the CNSP must rely on its internal staff for program most of its evaluation, advice and advocacy activities. Therefore, such valuable program endeavors as long-term follow-up and program expansion may not be easily developed. The Review Team, while generally impressed by the extensive network of laboratories, the availability and support of subspecialty services, and comprehensive educational and evaluative efforts, strongly supports the idea of a multi-disciplinary external advisory committee to provide input into program decision making and to assist in external advocacy efforts.

2.1.2 Assessment of its capacity to handle >540,000 newborn blood samples to be screened for genetic conditions including metabolic disorders and its ability to screen for additional conditions as scientific data supports its value.

The experiences in the CNSP to date indicate that essentially all California newborns receive adequate newborn screening services as prescribed in the statutory requirements. From the materials provided to the Review Team, it appears that specimens are collected, transported to the various laboratories, analyzed and reported in a time period consistent with the accepted practices in newborn screening around the country. There are currently 8 contracted laboratories and their combined capacity sufficiently provides for testing all of the 540,000 births in the state. As previously noted, this testing capacity may well be more cost efficient if some of the testing laboratories are consolidated.

Expanded testing is scheduled to begin later in the year and the sufficient equipment has been obtained to provide for these services. Based on conversations with the laboratory supervisory staff during this review and a visit and interview with staff members at one of the contract laboratories, each of the laboratories currently preparing to provide the testing service has sufficient space, equipment and personnel to provide expanded testing in an appropriate way. Some personnel who will be involved in the testing have already obtained training and others training for others is currently in progress. Given the history of the CNSP in implementing new procedures over the years, and the manufacturer's support that accompanies installations and new start-ups of this kind, it is anticipated that sufficient capacity will be in place, and quality testing will be offered, prior to the implementation date specified in the enabling legislation. A yearlong pilot program at the GDL has provided the necessary background for CNSP staff to provide the oversight and assistance that will be required when the program begins.

In considering capacity, there must also be consideration given to the follow-up activities that accompany interpretation and reporting of out of range and unsatisfactory testing results. Follow-up personnel are generally located in or near medical centers that provide subspecialty support for metabolic disease, thus it is likely that the needed support system is in place to meet the demands of the program expansion. Additionally, several staff members from the CNSP have attended the MS/MS training courses co-sponsored by the NNSGRC, HRSA, CDC, and APHL. These courses are designed to provide training for selected staff members who in turn are expected to assist in training others on their staffs. Assuming that this is the case in California, then sufficient expertise appears to exist to meet the follow-up demands expected. Based on the experiences of others, it is anticipated that the recall rate will be approximately 0.3% of all newborns undergoing screening using MS/MS techniques.

2.1.3 Efficiency

The current CNSP consists of 8 contract laboratories and 7 follow-up centers. There is centralized oversight from the GDL in Richmond. While there is little question about the efficiency and speed of decentralized follow-up in California, some questions exist relative to the cost efficiency of the decentralized laboratory testing system (see Section 2.1.1). It is essential that screening results be available as quickly and accurately as possible, and that short-term follow-up occur as rapidly as feasible so that confirmatory testing, diagnosis, and treatment can take place before there are any ill effects of the condition on the patient.

The CNSP is one of only a few programs that has contractual arrangements with diagnostic laboratories to provide confirmatory laboratory testing. However, incidental to this review, it was reported by at least one hospital that their hospital laboratory outsourcing contract does not allow that particular hospital to send their repeat tests to the contracted laboratory for at least

one of the conditions. It is not known to what extent this practice might be influencing whether the contracted diagnostic laboratories receive all newborn screening specimens. It is suggested that a study of hospital practices relative to use of the contracted laboratories might be informative, if these data do not already exist.

Currently the GDL provides repeat screening for PKU. It is likely that a laboratory capable of performing confirmatory testing for the conditions detected through MS/MS testing (including PKU) will be needed and this laboratory might possibly be used for PKU monitoring. The GDL previously provided repeat screening for newborns moderately elevated TSH levels as an alternative to serum testing. This procedure recently changed, and currently all newborns with an elevated TSH are referred for serum confirmatory testing. The Review Team suggests that these data be closely monitored to determine if the 'refer all' strategy currently employed is cost efficient, since the number being referred may be significantly higher than with the previous policy. Additionally, with the addition of CAH testing to the screening panel, the endocrine confirmatory testing contract will also need to include confirmatory testing for 17-OHP. The use of multi-tiered cutoff levels for CAH based on birthweight should provide an efficient initial screen and it will be interesting to see how effective the second-tier MS/MS procedure being implemented will be. For asymptomatic CAH cases with persistently elevated 17-OHP levels, it is suggested that the data from the Texas program be reviewed and a protocol involving ACTH stimulation testing be considered.

2.1.4 Past history, experience and ability

The CNSP began expanded testing beyond PKU in 1980 and during the intervening years has screened well over 10 million newborns. As noted in the 10-year data given in Section 1.0.0, and estimating an accumulation of another 50% of total patients since then, the program has now detected over 4,000 newborns with significant conditions that likely would have resulted in serious morbity or mortality without the newborn screening program. These screening efforts have proceeded with minimal evidence of difficulties over the years. When situations were encountered and program improvements were necessary to strengthen the screening system, they have been made.

The CNSP is an outstanding program and is considered one of the stronger and more comprehensive programs in the country. It is one of the few programs with a physician serving as the program administrator, and the varied support services within the program, including program evaluation, laboratory, follow-up, and education, are worthy examples for other programs. The extensive MS/MS pilot project in 2003 provided useful program information that should prove extremely beneficial in implementing expanded metabolic screening during the coming year. Likewise, the subspecialty resources available within California for both GAL and hemoglobinopathy reference services have allowed the CNSP to

develop models of subspecialty follow-up services in other areas of newborn screening, which are being utilized as models for other newborn screening programs across the country.

2.1.5 Communication with specialists, primary care providers, and families of affected infants

Within the newborn screening system, there are many different stakeholders including subspecialists, primary care providers and families. It is essential that there be open lines of communication at all levels and that the information transmitted be timely, informative, and effective. The utilization of ASCs and extensive educational resources appears to adequately meet the communication and educational needs of all parts of the screening system. The program website provides a valuable communication/education resource that can be expanded to include numerous pieces of program information and extensive educational materials. In addition to current information available on the website, future materials might include disease specific newsletters, annual reports, advisory committee meeting announcements and meeting minutes, and more extensive disease-specific educational material and linkages.

An active parent support network is known to exist for PKU, but the extent of other parent support activities is not known. As CAH and other metabolic conditions are added to the screening program, expanded opportunities for parent support activities will exist. Similarly, there appear to be parent activities for hemoglobinopathy patients available through the subspecialty center at Oakland, but the Review Team does not know the extent of services in other areas of the State. It would appear that this is an area in which additional efforts of the ASCs might be appropriate. Dedicated space for different screening conditions or groups of conditions on the CNSP's website may offer an easy opportunity to provide expanded parent support. Examples of disease-specific newsletters for parents that might serves as models exist in both the Washington and Texas programs.

2.1.6 Documentation

The Review Team was provided considerable information about the procedures for both the laboratory and follow-up/administration/education aspects of the CNSP. A manual system of documentation currently exists in most areas of the program, and the records being kept appear appropriate. All laboratory documentation must be kept in a method appropriate for achieving laboratory certification, and the records reviewed at both the GDL and the local Kaiser contract laboratory appeared to meet all record-keeping standards. While the record keeping activities of the follow-up centers were not specifically reviewed, the procedural materials provided to the Review Team appear to document appropriate protocols for necessary record keeping. Additionally, since residual blood spots remaining after completion of the analytical processes for newborn

screening are stored for an extended period of time, the records necessary to access these specimens efficiently require a logical means of storage and retrieval, and these appear to be in place. A computerized tracking system currently being implemented will provide a more efficient electronic means of record keeping, and when implemented the system in operation should be carefully reviewed to ensure that it meets all relative record keeping requirements. Consideration of patient privacy must be an integral part of the system and all records must comply with pertinent security measures and genetic privacy statutes and rules.

2.1.7 Educational materials for patients and provider

The educational materials available through the CNSP are extensive. In addition to the standard brochure of information for parents, there are numerous examples of quality disease-specific information. Most materials appear to be available in several different languages reflecting the diverse population groups within California. The information that appears to be available through GeneHELP is also extensive. The CNSP website (http://www.dhs.ca.gov/pcfh/GDB/html/NBS/Mainmenu.htm) provides basic information for both healthcare professionals and parents. There are links to several other sites to provide choices for information on specific conditions and information about expanded screening and the status of the program are readily available. While several newsletters with program information were accessible on the website, the last was in 2003. The lack of availability of previous newsletters indicated that there was no real schedule as to when program newsletters might be published. Comprehensive summation reports of program data were also not readily available.

The Review Team suggests that the program's website provides a ready means of information distribution, and that newsletters and annual reports are materials worth publicizing in this way. While some of the articles published by program personnel describing research and other program activities were referenced, none were readily available in pdf format (or alternatively through linkages to periodical websites). This, too, might be an activity worth pursuing. That is, a specific location within the website might be dedicated to access to published material originating from CNSP staff. Additionally, as other materials become available as a result of the recent HRSA/ACMG report *Newborn Screening: Towards a Uniform Panel and System* (e.g. fact and act sheets for healthcare professionals), these might also be effectively made available on the website. GeneHELP is also not currently available on the website. Thus, requests for educational materials available on GeneHELP must currently occur through telephone contact with program educators. Access to GeneHELP through the website also seems to be a worthwhile pursuit.

2.2.0 Technical Review

2.2.1 Quality Control and Quality Assurance

Often quality assurance is mistakenly assumed to apply only to laboratory testing; however, many program elements outside of the laboratory can, and should, be monitored for quality. The quality of the entire newborn screening program should be periodically evaluated. As an example, the quality of received specimens can be judged against established criteria by monitoring unsatisfactory rates. Completeness of demographic data can be documented as can the time required to receive repeat specimens and the time from specimen collection to location and treatment of presumptive positive patients. Program coverage can be judged by comparing birth records and patients screened. Many of these parameters are best judged at the point of specimen receipt and so a contracted laboratory would need to have such parameters specified in the contract for monitoring. All of these items appear to be in place in the CNSP. In fact, evaluation of program quality appears to be the specific responsibility of the Program Development and Evaluation Section. Laboratory quality assurance appears to be a joint responsibility involving the GDL and the Program Development and Evaluation Section.

Documentation of adherence to established program protocols and corrective actions taken when failures occur are essential components of the quality assurance process and should be aimed at improving overall program quality. Setting criteria for follow-up performance based on an internal operations manual, and documenting time limits for accomplishing these criteria form the basis for most quality assurance programs, and California's is no different. Various disorder-specific protocols for follow-up have been established and are available in an operations manual. Time lines included in any of the standard operating procedures for follow-up appear to be realistic (as opposed to idealistic) and include appropriate end points and corrective actions in case of failures. Periodic audits should be carried out among the various contracting ASCs to complete process, if they are not currently being performed.

Consider an annual review of patient treatment compliance and status. Physician advisor(s) who can provide professional judgment on treatment issues should best be able to give advice on treatment reviews. Likewise program advisors or an advisory committee can give useful advice on other quality indicators. They can also assist the program in assessing data obtained to evaluate program quality. A California Newborn Screening Annual Report should be considered. An example of such a report from Nebraska is included in the Appendix. It should provide program visibility and be a valuable information source for those who might be interested in program accomplishments. Statistical data of program performance can be graphically displayed and can provide easily viewed summaries of program experiences. From year to year these summaries can provide a measure of program accomplishments and improvements. This report should also be available to the public via the website. The CNSP and Dr. Fred Lorey are to be specifically congratulated for their efforts to provide extensive program evaluation data to the national dataset. Continued cooperation

in this way provides meaningful evaluation data not only for internal program use, and comparisons between programs, but also as an aid in understanding screening population issues at a national level (incidence, etc.)

It is suggested that CNSP coordinator perform a periodic systems' analysis to identify any gaps in the system and if gaps are identified, they should be corrected. Continuous oversight and monitoring is necessary to assure that quality is maintained. This oversight can best be achieved by ensuring that quality assurance continues as a responsibility of the all sections within the GDB, and that various quality assurance requirements continue in the contracts with the screening and diagnostic laboratories and with the ASCs.

Over the years the GDL has provided a quality assurance program to ensure that quality of the filter paper collection devices used by the program. Initially this service was provided because there were concerns about the quality of the paper and its potential for adversely affecting analytical procedures if there were quality variations, particularly with respect to uniform absorptivity. Over the years there have been vast improvements in the quality assurance activities of both the filter paper manufacturer(s), who must meet FDA or equivalent requirements since the device now falls under the FDA product requirements, and the newborn screening community (through activities of CLSI/NCCLS and CDC). The Review Team suggests that the necessity for this quality assurance effort be reviewed and consideration be given to its discontinuation if the other activities now in place provide sufficient quality assurance efforts to satisfy the CNSP's needs. At the current time, the CNSP is the only program to our knowledge continuing to engage in this activity.

2.2.2 Reliability and reproducibility

One of the measures of reliability and reproducibility stems from performance on daily quality control materials and another is from performance on outside proficiency testing challenges. The GDL monitors the daily quality control performance for the contract laboratories and individual laboratory performances on CDC proficiency testing challenges. The procedures currently in place for ensuring day-to-day reliability and reproducibility appear to be satisfactory and are maintaining appropriate quality of testing in this regard. However, it was noted that current laboratory protocols do not require a check of reproducibility of the results of individual sample analyses, particularly as they relate to results considered outside of the expected range. It is standard practice in all other newborn screening laboratories with whom the Review Team has had contact (over 30) that all results outside of the expected range on initial testing are reaccessed and retested in order to verify the initial screening results. This reverification serves two primary purposes. First it confirms that the specimen initially thought to be tested was indeed the specimen tested (i.e. a punching error did not occur). And second, it serves to validate the reproducibility and reliability of the assay being performed. When a test result discrepancy is found, then

various protocols must be followed in order to ascertain the reason for the discrepancy. In cases where a discrepancy cannot be resolved, the conservative approach is to report the results as invalid, with a request for an additional specimen.

Personnel at the contract screening laboratory visited were asked to what extent initial screening results were validated by results on recall specimens. The response indicated that from time to time unexplained reproducibility problems occurred. Occasional discrepancies that could not be resolved through GDL investigations appeared to be written off as "fliers" that sporadically and spontaneously resulted from unexplained technical issues likely caused by instrumental anomalies. In fact, these unexplained differences in results between screening and confirmation may have resulted from punching or other clerical errors, including hospital errors in patient identification. The net result is a recommendation from the Review Team that the laboratory testing protocol include a reaccession and reanalysis step (preferably by a different technique) prior to release of screening test results. Results of an in-house survey in the New York screening laboratory aimed at identifying misidentification of newborn screening specimens by submitters (perhaps as high as 1 in 400) confirms that a clerical error on the part of the submitter may also offer a reason for lack of agreement between screening and recall results.

2.2.3 Diagnosis, management, follow-up and counseling

Diagnosis, management, follow-up and counseling are important components of the overall newborn screening system. When newborn screening results are available, it is essential that they be transmitted quickly and that follow-up services are in place to ensure that all newborns identified as possibly at risk for a condition receive confirmatory testing. In the CNSP, this occurs through communications to the ASCs by contract laboratories to ensure first that patients needing to receive recall testing obtain such testing in a timely way, and second, that confirmatory testing occurs so that appropriate diagnosis and management occurs before any adverse health consequences. In some cases, counseling may be appropriate and /or necessary including dietary counseling for metabolic conditions, genetic counseling, and other family counseling related to understanding the meaning and impact of results obtained.

All of these elements noted above appear to be in place in the CNSP. The current decentralized follow-up system using community-based resources appears to rapidly and effectively reach the 'at risk' population effectively and efficiently. Contract oversight by a central authority and reporting to a central authority seem to provide good communication and effective contract management. From the limited experience of the Review Team in reviewing one of the Kaiser follow-up activities, the program appears to be functioning well and meets the needs of the population. Qualified counselors and subspecialty expertise is available and good tracking systems appear to be in place.

a. Organizational and individual responsibilities for medical, laboratory, and follow-up

As previously noted, the CNSP contracts with community-based ASCs for follow-up and tracking services. This system allows for quicker tracking services in the local area should it become necessary for an individual newborn to receive extensive follow-up services as a result of noncompliance with a recall request. It also allows for local accountability for all follow-up activities, including timeliness of follow-up activities. The CNSP organizational infrastructure assigns contract coordination to Ms. Velazquez and follow-up data ascertainment and evaluation to Dr. Lorey. Both are to be commended for their job performance. All of the follow-up activities appear to be appropriately in place and working. Similarly, Dr. Sherwin is to be commended for his activities in ensuring quality laboratory services both as the screening and diagnostic level. Dr. Cunningham's activities within the medical community are also to be acknowledged and commended since his medical leadership is primarily responsible for program medical decisions.

2.2.4 Consolidation of newborn screening program

As previously noted, the Review Team agrees that there is likely room for laboratory consolidation given the current workload of the various contracting laboratories. This would likely result in operational cost savings since some of the equipment currently being used are not used to their maximum capability. Likewise manpower savings will proportionately increase as greater efficiency is realized by combining laboratories. On the negative side, consolidation will likely mean increased demands on the contractor relative to space and environmental conditions, and the redundancy (back-up capabilities) provided by 8 laboratories would be decreased somewhat.

Consolidation of the follow-up services, on the other hand, does not present the same savings. In fact, their local availability of follow-up personnel provides faster access to patients and provides a more efficient and effective means of interacting with local birthing facilities. The decentralized approach currently in place allows for individual birthing facility visits once in every two-year period and provides for closer collaborations between contractors and facilities. One of the keys to successful decentralization is strong central oversight and coordination, and this appears to be the case in California. Coordination of the ASC contracts by the Newborn Screening Section and coordination of the data obtained by the Program Development and Evaluation Section appear to provide appropriate management and evaluation of these decentralized follow-up activities.

Little has been mentioned about newborn screening for hearing loss, even though it is included in the ACMG newborn screening discussions. Many state newborn screening programs have developed consolidated hearing and blood spot screening as a more efficient way of providing patient services. While California is a large state, and this allows for easier development of self sufficient program infrastructure when new programs are implemented, there are often lessons to be learned from other programs with similar service delivery goals and populations. Indeed this is the case with newborn screening programs for hearing loss and other congenital conditions such as those included in the GDB mission. Where total newborn screening consolidation is not possible, then data consolidation and integration should be an active consideration. The Review Team strongly encourages continued consideration of the possibilities of consolidated data management and program integration between the newborn hearing screening (NHS) and the dried blood spot (DBS) screening programs.

In order to have the most impact in improving child health, it is becoming more common to consider the possibility of shared information between the public health and clinical domains. Access to public health information, such as screening results and service encounter information, would likely be more useful if readily available at the point of care, i.e. the child's medical home. Currently, very few public health data systems allow this to occur and privacy issues are often a confounding issue. To address some of the immediate information needs of healthcare providers, some programs use such mechanisms as voice response systems. In newborn screening programs, voice response systems can verbalize newborn screening laboratory test results or testing status so that this information is available 24 hours a day, 7 days a week (24/7). Voice response systems of this type typically have the capability of faxing a hard copy of the basic testing results on demand. In this way, physicians or others with the proper security clearance, can access patient screening results as they are needed, such as at the hospital late at night or on holidays.

While voice response systems may fulfill some of the primary healthcare practitioner's needs, they only augment child health data systems, and there is still a need for access to more comprehensive medical information. Integrated information systems are being developed in public health departments so that data duplication is minimized and basic client information is available to multiple programs from a single information source. Ultimately, such information will become available to healthcare providers through the Internet or downloadable into an electronic health record on the desktop or a personal information device.

The newly acquired data system in the GDB appears to meet the some of the newborn screening system needs well. There is a pressing need for an electronic data feedback system from the subspecialty providers to the C NSP and this is planned. The Review Team encourages rapid implementation of this data feedback/management system.

Some newborn screening programs have realized that information obtained at birth from DBS screening can become an integral part of integrated health information systems. Other useful data might include immunization status, NHS status, Children with Special Health Care Needs (CSHCN) Program, Women, Infants, and Children (WIC) Program and various other CDHS program-related information. Additionally, in order to ensure full population coverage in newborn screening and to validate demographic data, integration with birth certificates is desirable. A number of states are now developing integrated information systems. These systems contain a central repository of certain data elements that are consistent among the different programs, such as the basic patient demographic information - name, date of birth, sex, race/ethnicity, etc., and allow data sharing with other program-specific data systems.

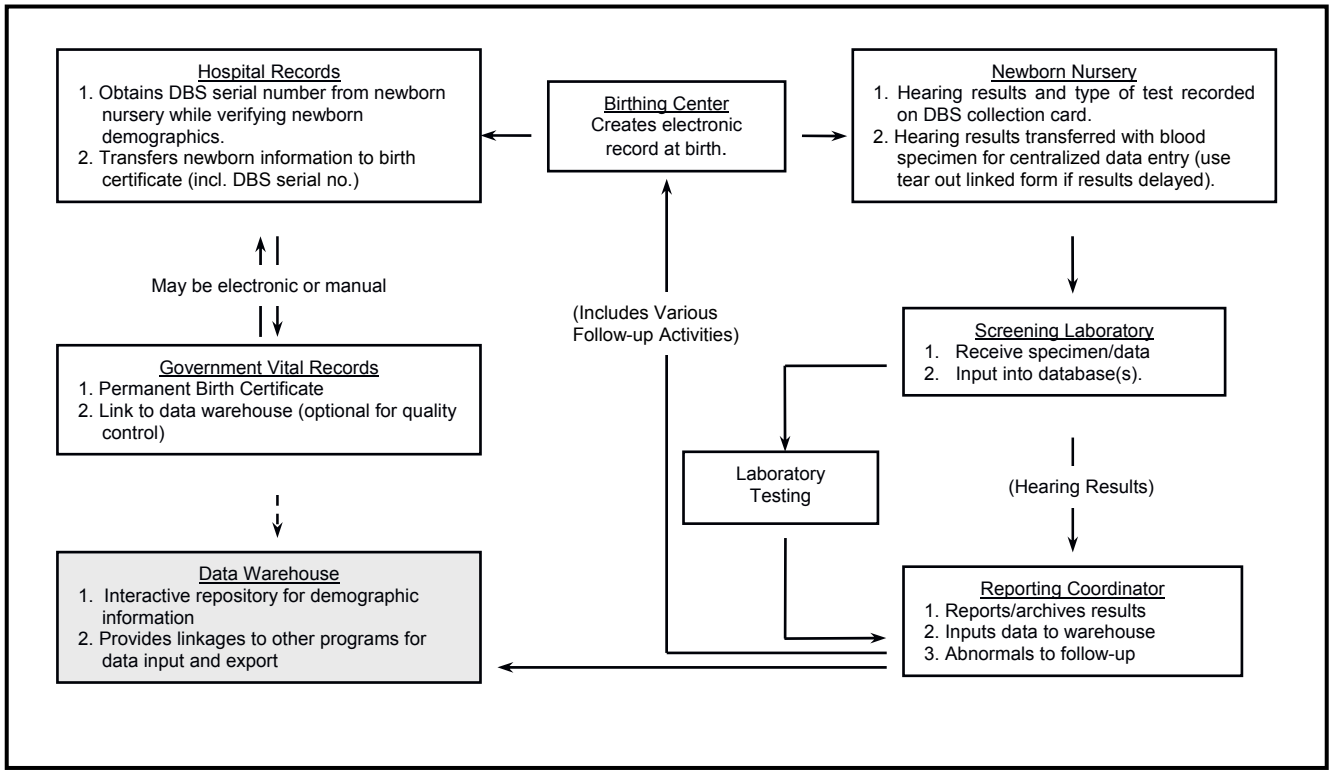
An integrated database of this type can be envisioned as a wheel and spoke arrangement. In the center of the wheel is the central repository of general patient demographic information with spokes branching out to program specific data or information. If the design is well thought out and planned, then the demographic information can be specific and comprehensive enough to meet the needs of virtually every program and result in a comprehensive integrated record for an individual child, i.e. a child health profile. In such a system, patient demographic information can be input by the program having the first patient encounter. Subsequent programs would first inquire to see if the information were available and current before duplicating the data input. Program specific data would be maintained in a secure fashion accessible only to those designated users within the program or within the public health agency.

As an example, the patient demographic information required for NHS follow-up is similar to that required for routine newborn DBS follow-up. The minimal data elements suggested for DBS newborn screening are specified in a national standard (now in its fourth revision) and are limited to the essential data elements needed for identifying patients considered at risk as a result of screening (see CLSI/NCCLS LA4-A4). Already captured in most DBS databases are: infant's name, address, phone number, physician of record, physician's phone number, etc. The same essential data are required for follow-up of newborns with a congenital hearing loss and therefore both programs should be able to utilize the same demographic database (see Figure 1).

By limiting the information captured on <u>all</u> patients to the essential elements needed to identify and locate the patient, the amount of data entered in the central repository can be streamlined. Case specific information on the small number of patients with abnormal test results can be obtained and entered as part of the follow-up process. Limiting the case specific data in this way adds to the overall efficiency of the data collection/data entry task by leaving non-critical information to be obtained later on the less than 1% of patients for whom it is needed. Thus, for example, additional data elements specific to hearing loss could be recorded in a program specific case management database (or other appropriate

file), in a process similar to that generally employed in DBS newborn screening follow-up. In cases where a screening program may wish to monitor risk factors for all patients, additional data elements could be added to the DBS form, entered along with the demographic information, and stored in a separate program specific database. However, care must be taken to ensure that the information anticipated from additional data of this type is valid and useful, since data entry expenses will be increased by any additional information that must be input.

Figure 1. **Diagram of newborn screening data flow using the warehousing concept and linkages with vital records as a means of ensuring that all newborns receive both a newborn screen and a birth certificate.**



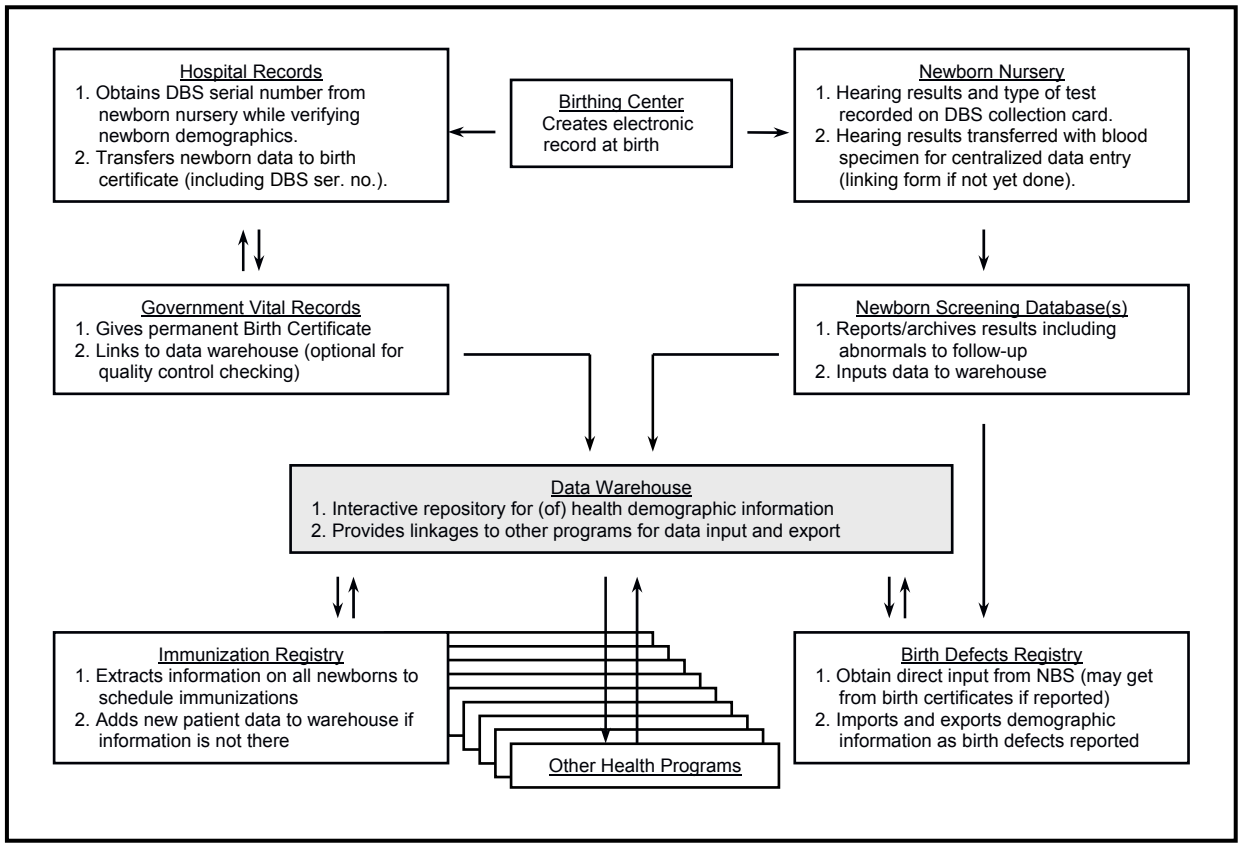
Timely information available from DBS and NHS programs could also provide demographic information useful for birth certificates, as shown in Figure 1 (left-hand side). If newborn screening data cannot be used to populate the birth certificate database for technical or logistical reasons, they can still be valuable as a quality control check to ensure that birth certificates exist for each newborn receiving a newborn screening test. Reverse validation may also be beneficial in assuring that each recorded birth has received an appropriate newborn screening test (although programs should be sensitive to the fact that birth certificate information is not collected to be used punitively). Because most of the DBS conditions require earlier identification in order to ensure optimal outcomes, a quicker match is needed if the birth certificate is to be useful for ensuring 100% screening coverage. While this delay may not be the result of the matching process, an alternative to the current practice is the use of the DBS serial number.

This unique identifier (described in CLSI/NCCLS LA4-A4) can provide a simpler, unique and readily available identifier to link birth certificates, NHS and other child health and vital records programs together as long as a field for this number is included in each linking database.

As NHS expands in California, data management needs will increase. It may be useful to consider the feasibility of using the new DBS computer system to capture NHS data in order to assist in meeting these data needs. Both newborn screens (NHS and DBS) occur before the newborn leaves the nursery and both programs utilize essentially the same patient demographic information. Submission of limited hearing screening data with the newborn screening form provides an easy way of quickly obtaining hearing information on each and every newborn in the state. Integration of these data into a centralized follow-up/service management system can be facilitated by this combined data approach and ensure the timely follow-up of those newborns who need to be followed up. Data integration through combined NHS and DBS data elements on the DBS screening form has already been accomplished in over 15 states and the "lessons learned" in these experiences should prove useful in any similar considerations in California.

A truly comprehensive consolidated (integrated) newborn health information system would theoretically include mechanisms for integrating initial patient information from any program that may have the data available, whether or not it originated in a newborn screening encounter [see Figure 2]. Thus, for example, if a child was to be given an immunization, an inquiry of the central repository should indicate whether or not there was basic demographic information available, and additionally whether or not there was an immunization history. If demographic data were missing, then they would be input at that time and would be available for future inquiries, whether or not the inquiry originated with the immunization program or not.

Figure 2. Diagram showing data flow into and out of a data warehouse, with particular attention to interactions with newborn screening, birth certificates, immunization registries, and birth defects registries.



Consideration of this type of consolidated and integrated system, or expanding to other child health programs, may provide food for thought as computerization continues to move forward within the CDHS. Building upon the successes of various data systems within CDHS is a logical progression towards improved patient care and should be strongly considered. Useful references discussing current public health information activities may be found in the Appendix of this report and also in a special issue of the Journal of Public Health Management and Practice, November 2004 Supplement.

2.3.0 Program Evaluation

The Institute of Medicine (*The Future of Public Health*, National Academy Press, 1988) has previously defined the core elements of public health as assessment, policy development, and evaluation. Likewise, the newborn screening system has been defined (Molecular Genetics and Metabolism 2001:74;64-74) as consisting of 6 principle components, education, screening, follow-up, diagnosis, management, and evaluation. Critical to program evaluation is data collection and analysis.

2.3.1 Data collection and analysis

The California genetics and newborn screening programs have long been recognized as leading proponents for maintaining and analyzing comprehensive program data. Dr. Cunningham was the primary advocate who encouraged the Council of Regional Networks for Genetic Services (CORN) to become active in national data collection efforts in the late 1980s. Since 1988, national newborn screening data have been collected and these data have expanded over the years until today there is a comprehensive On Line data reporting system for newborn screening information. The CNSP was one of the beta test sites for this system and Dr. Lorey and Dr. Sherwin, in cooperation with Ms. Velazquez and others, continue as active contributors to the national data set.

In order for a newborn screening program to maintain its quality, efficiency and effectiveness, the data accumulated within the program must continually be analyzed and compared to others involved in similar activities. The CNSP is a model for including this program component in its everyday activities. Because of California's large newborn screening population, data collection and analysis are significant challenges. It appears that the these program components have been given sufficient and appropriate recognition within the CNSP so that up to date data comparisons are available for program evaluation as needed. Thus, it is possible to monitor detection rates, timeliness of various newborn screening services, appropriateness of analytical methods and cutoffs, etc. so that program evaluation can be an ongoing activity. From materials presented to the Review Team and from personal observations, it appears that the data collection and analysis efforts throughout the CNSP are both sufficient and appropriate to provide for continuous quality improvements within the program. Dr. Cunningham and Dr. Lorey are to be particularly commended for their recognition of the necessity for quality data and the analytical uses that can be made of these data.

2.3.2 Long term tracking and outcome evaluation

Long-term tracking and follow-up begins with the confirmation of a diagnosis and continues throughout the life of the individual. It is important for newborn screening programs to collect program evaluation data on the long-term outcome of individuals identified by screening. These data provide a mechanism for determining the effectiveness of newborn screening system and should provide information on which to base program changes and policy development. Long-term follow-up data are a critical need for most newborn screening programs, including the California program. Without outcome data, it is impossible to accurately assess the program's performance, one of the core functions of public health (assessment, assurance and policy development). From information available to the Review Team, it appeared that long-term tracking and outcome evaluation were areas of need in California, and areas that could be emphasized as program expansion occurs. The massive amount of screening data available in California presents an opportunity to contribute immensely to

understanding the natural history of most of the conditions included in the screening program. Current long-term follow-up appears limited to efforts in maternal PKU and mandatory reporting of some limited information on PKU cases for the first 5 years of life.

Collection and evaluation of long-term outcome data are strongly recommended as part of the follow-up responsibilities of the program, and the medical management centers. Long-term outcome data can be accumulated through annual inquiries either to the primary care provider, to the consulting subspecialist (if one exists), or to the parent. Since long-term outcome follow-up will invariably require funding if it is to be done correctly, it is suggested that this be a consideration of any deliberations regarding the program fee. The CNSP seems well positioned financially with authority to charge a fee and a dedicated account into which it flows.

Long-term outcome data on the impact of newborn screening are scarce. Particular emphasis has been placed on PKU since dietary compliance for women with PKU is especially important during pregnancy, and since other adverse affects of non-compliance with dietary therapy have been demonstrated in persons not maintained on treatment for life (the reader is referred to: *Report of the NIH Consensus Development Conference on Phenylketonuria: Screening and Management, October 16-18, 2000*. National Institutes of Health, Washington, D.C., February 2001). Apart from selected research studies on some of the other disorders included in newborn screening programs, particularly for congenital hypothyroidism, most newborn screening programs have not maintained long-term follow-up data. A recent report on newborn screening outcomes in Georgia (Van Naarden BK, Yeargin-Allsopp M, Schendel D, Fernhoff P. *Long-term developmental outcomes of children identified through a newborn screening program with a metabolic or endocrine disorder: a population-based approach*. J Pediatr;143:236-42 - see Appendix) supports the importance of maintaining these types of data. Wherever possible, outcome data should be maintained as long as possible in order to ensure availability of, and compliance with, prescribed medical treatment programs, and to provide the valuable program evaluation data needed to justify the continuation and expansion of newborn screening activities. The process of obtaining and maintaining long-term information has been made more complex by the national focus on privacy and recent passage of federal and state privacy legislations, including the Health Insurance Portability and Accountability Act (HIPAA). Nonetheless, long-term outcome data are essential for program evaluation and provide a mechanism for documenting that affected children are receiving needed services in a timely way.

Some programs have found it productive to use their advisory groups as proponents and contributors to long-term outcome tracking, another possible reason for the CNSP to consider an advisory committee. Such a committee can be extremely helpful in developing data elements to be evaluated over time for each condition. In some cases, these data may find use in various research

purposes and program consultants should be apprised of this opportunity. It is important that any new conditions, such as those soon to be added to the CNSP, have long-term outcome data collection included in their implementation. It is much easier to begin collecting data prospectively with new disorders than to establish it for disorders currently in the program, and for which there is little enthusiasm for documenting successful outcome (having already been established in most people's minds, whether or not it has been established to the satisfaction of the policy makers). Some of the data that might be collected long-term include:

- Age at definitive diagnosis and initiation of treatment for each disorder.
- Demographic and clinical profiles of the patients under treatment.
- Mortality and morbidity measures for each disorder.
- Measures of compliance with treatment protocols.
- Measures of long-term outcome and functionality of patients (schooling, employment, psycho-social adaptation, reproductive success, etc.).
- Costs associated with treatment.

2.3.3 Cost Benefit Analysis (Comparing costs with costs avoided and other state program costs which include that of contracting with private organizations).

Few sound and comprehensive cost benefit studies of newborn screening systems have been published. To quote from the ACMG Report, "Some studies have focused on the short-term costs and benefits of the screening stage and the immediate steps following the identification of a screen-positive infant. Most address tests for only a small number of disorders, and none has explored the cost savings and clinical benefits of tests such as MS/MS."

The ACMG Report notes that a more in-depth cost-effectiveness study was performed as part of the contracted work that will be published. The ACMG Report notes that:

> "*The results of these analyses indicate that all newborn screening programs evaluated improved outcomes and most reduce overall costs. Screening for CAH added increased cost per QALY gained, but the cost was well within the range conventionally considered cost effective. Screening for galactosemia was the only strategy that would be considered not cost effective in the base case analysis. However, under some reasonable assumptions, it can be shown to be cost effective. The identification of potentially affected individuals at such an early time in life leads to many years over which the benefits accrue and, in aggregate, the benefits outweigh the costs."*

"Technologies such as MS/MS further save money due to their multiplexing capability and low screening false-positive rates. MS/MS, used to screen for multiple conditions, had the greatest impact on outcomes and saved the greatest amount of money in the analysis. Virtually all screening for conditions that are treatable with significantly beneficial outcomes can be justified with benefits increasing as more conditions are included. The analysis also showed that clinical benefits and savings depend on low false positive rates and timely follow-up and treatment of positives, emphasizing the importance of an integrated screening and follow-up program."

In terms of costs for utilizing the California model of public/private partnering for laboratory testing and contractual follow-up centers versus a single source contract for private laboratory testing, it is doubtful that cost differences would be significant. This is based on the understanding that the California model currently utilizes some private and some public partners, and it is difficult to understand how a model of only private (for profit) services could be more cost efficient. Answering this question in depth would require detailed cost accounting of the California program versus a similar accounting from the private source. Care must be taken to compare likes to likes such that laboratory is compared to laboratory and follow-up/education to follow-up/education, etc. In most screening programs, the cost of laboratory testing alone is less than 50% of the total program cost, given the large amount of financial resources needed to adequately fund the follow-up, education, and other ancillary costs of the program including limited medical treatments. The reader is referred to Table 2 presented earlier, which details the fees currently charged by other newborn screening programs, and the 2003 report of the Government Accounting Office, *Newborn Screening: Characteristics of State Programs* (available online at http://www.gao.gov/new.items/d03449.pdf).

3.0.0 Other Considerations: Comparison of California Newborn Screening Program with other states for areas of strength and improvement

3.1.0 Advisory Committee

The Review Team believes that a formal advisory system is important for all newborn screening programs. This is reinforced in other guidance about newborn screening (*Screening* 1992;1:135-47 and *Pediatrics* 2000;106:383-427). If the program is to serve the community well, it must seek outside advice from community representatives. The CNSP is one of only 2 programs in the U.S. that reports no formal external advisory group. Across the country, programs have adopted various models for their advisory systems, most of which center around a single program advisory committee. However, in large states, multiple committees or multiple subcommittees have been necessary in order to accommodate input from the larger numbers of subspecialty providers (e.g. hematology committee, endocrine committee, etc.). The most

effective committees have multi-disciplinary representation and usually include members both from within and outside of government.

An example of government programs that might be represented on a newborn screening advisory committee include the Medicaid Program, the Department of Insurance, Department of Education, the Birth Defects Program, the WIC Program, the CSHCN Program, and the Newborn Hearing Screening Program. Possible non-government members should include broad representation from newborn screening stakeholders including, for example, primary care physicians, obstetricians, the Medical Association, the Pediatric Society, the Hospital Association, nurses, nutritionists, genetic counselors, a representative from the insurance industry, community activists, subspecialty physicians with an interest in newborn screening (such as an endocrinologist, hematologist, metabolic disease specialist, and pulmonologist), business men or women, and may also include legal, ethical and religious representation. Most newborn screening advisory committees have found it essential to include several lay advocates - individuals with disorders detectable by newborn screening or members of families of affected individuals. It is generally agreed that committee staffing should be provided by the program and interested follow-up, administrative, and laboratory personnel should be encouraged to attend meetings to provide technical information. However, in order to achieve the goal of obtaining outside program advice, CNSP personnel should not have a formal role in committee deliberations or voting. It may be also be useful to have an internal advisory committee that includes personnel and subspecialty consultants to guide program operations.

The Newborn Screening Advisory Committee should meet regularly and formally, with an appropriate agenda that includes brief descriptions of the issues to be discussed. The agenda should be available to members well in advance of committee meetings. Minutes should be a part of the formal process and should be widely and actively distributed to any interested party following each meeting. TNSP staff should assist with scheduling, agenda preparation, travel arrangements, etc. Teleconferencing and/or videoconferencing are options for some of the meetings in order to decrease costs, but it is generally agreed that at least one face-to-face meeting annually is desirable. It is essential that the committee understands and agrees to its role and its rules. There must be a clearly stated mission that includes a defined committee role and process for communication with the program. Most programs have found that a strong independent chair with standing in the medical or consumer community is helpful. Some programs have used committee co-chairs to help ensure that personal agendas do not compromise the committee's effectiveness.

A functional Advisory Committee can be a powerful advocate for the program. The Committee can be asked for advice on adding or subtracting conditions to the screening panel and other important cross-cutting issues such as financing. The Committee may also be useful in providing advice on many other program issues including legal and ethical issues, public relations, professional and consumer education, interactions with the health care community, and other program priorities. Program decisions made within the advice of outside advisors should lead to stronger support for

their implementation. Without participation from the community that provides program support (clinicians, hospitals, parents and families) then the program faces a continuing uphill battle for community acceptance.

In California, a formal Newborn Screening Advisory Committee would likely oversee smaller working groups or subcommittees (such as the current ad hoc groups) with specific interests such as hemoglobinopathies, metabolic disease, endocrinopathies, parent and professional education, and community/consumer affairs. Other ad hoc or standing work groups can be formed as needed - for example for consideration of parent issues, screening for cystic fibrosis, biotinidase deficiency, or lysosomal storage diseases. To promote and maintain active participation of advisory committee members, support funding should be available for travel to meetings, and such services as child care (particularly for consumer members). Any funds needed to support the work of the Advisory Committee or its subcommittees should be included in fee considerations.

3.2.0 Education of policy makers (e.g. Legislators).

One of the biggest challenges currently facing newborn screening programs is adequate and appropriate education of policy makers. It is essential that the CNSP continue to be proactive in addressing the newborn screening educational needs of California legislators. There are active advocacy efforts aimed at expanding newborn screening activities. While these efforts are usually complementary to the goals of local newborn screening programs, it has occasionally been the case that the information conveyed to government officials may not contain all of the information necessary for informed decision making. Thus, it is important for the CDHS to make sure that program and other scientific information needed for sound policy decisions are available to the policy makers. There are various means of getting the message out and it is important to consider the best mechanism for accomplishing this education in a timely way. It is important that the concept of a newborn screening system be conveyed since most often the message that has been received by government officials is that newborn screening is simply an inexpensive laboratory test. There is usually little attention paid to the fact that a truly comprehensive population-based newborn screening system must serve all of the population and must provide for an appropriate and timely medical service delivery system if it is to be effective.

Appendix 1 - Brief Resumes of Review Team Members (Alphabetical Order)

CURRICULUM VITAE

WILLIAM HARRY HANNON

ADDRESS

Newborn Screening Branch
National Center for Environmental Health
Centers for Disease Control and Prevention
4770 Buford Highway, NE/F-43
Atlanta, Georgia 30341-3724

EDUCATION

Georgia State University, B.S., 1965, Chemistry
University of Tennessee, Ph.D., 1972, Biochemistry
Oak Ridge National Laboratories, 1973, Post-Doctoral

PROFESSIONAL SOCIETY MEMBERSHIPS

Charter Member: International Society for Newborn Screening (ISNS) - 1987 Member of ISNS Executive Council (1999-present); Vice-President (2002-present)
Member of four other organizations

PROFESSIONAL COMMITTEES

1991-present	International Quality Assurance Working Group - ISNS
1991-present	Newborn Screening and Genetics Committee – CDC Liaison Association of Public Health Laboratories
1999-present	Newborn Screening Committee – CDC Liaison National Newborn Screening and Genetics Resource Center

Serves or served on 17 other national and international committees for quality assurance and/or standard developing committees for laboratory improvement.

EXPERIENCE

1982-present	Chief, Newborn Screening Branch, Division of Laboratory Sciences, Centers for Disease Control and Prevention

Among other duties, supervise the National Newborn Screening Quality Assurance Program providing dried blood spot proficiency testing and quality control materials, performance reports, and technical consultations to 352 newborn screening laboratories in 53 countries.

Employed by the Centers for Disease Control and Prevention since 1961.

PUBLICATIONS

Over 175 publications in scientific journals and proceedings with most of these concerning filter paper tests and newborn screening issues including: *National Standard for Blood Collection on Filter Paper for Neonatal Screening Programs*, National Committee for Clinical Laboratory Standards (NCCLS), approved standard, October 1997, and U.S. Newborn Screening System Guidelines, *Screening* 1992;1:135-47.

Author of 14 chapters in scientific books, over 75 abstracts and more than 100 presentations -- most by special invitation and related to newborn screening issues.

SPECIAL ACTIVITIES

Consultant – 2 international publications; *Screening* and *Infant Screening Newsletter*

Organizing committee - several National and International Newborn Screening Symposia

Co-author for 2 World Health Organization guidelines on Prevention and Control of Congenital Hypothyroidism and Phenylketonuria

AWARDS

Recipient of 12 Public Health Service special recognition and service awards including:

1989 - U.S. Department of Health and Human Services, Public Health Service Special Recognition Award for "Outstanding scientific leadership in development and implementation of a laboratory quality assurance which substantially contributed to the HIV Seroprevalence Survey in Childbearing Women".

1992 - Charles Shepard “CDC Preeminent Science Award” - Publication of the Year

1993 - U.S. Department of Health and Human Services, Public Health Service Centers for Disease Control, Superior Service Award for “Outstanding service in creating and maintaining a national infant screening quality assurance program and a center of expertise for dried blood spot technology.”

2000 - HHS Secretary’s Award for Distinguished Service for “Devising a new test strategy to detect early HIV infection that will greatly enhance HIV/AIDS surveillance and prevention programs.”

Recipient of the 1999 ISNS Robert Guthrie Award for “Worldwide recognition of outstanding contributions to newborn screening.”

CURRICULUM VITAE

MARIE YUEN MAY MANN

ADDRESS

5600 Fishers Lane
Parklawn Building, Room 18A-19
Rockville, Maryland 20857

EDUCATION

1971-75	B.A. Wake Forest University
1978-82	M.D. Tulane University
1987-88	M.P.H. University of North Carolina at Chapel Hill
1982-83	Resident in Pediatrics - Duke University Medical Center
1983-85	Resident in Pediatrics - Tulane Medical Center/Charity Hospital

PROFESSIONAL EXPERIENCE

1985-86	Physician, Adolescent Clinic, City of New Orleans
1985-86	Physician, Browne-McHardy Clinic, New Orleans
1985-86	Physician, Children's Medical Care Center, New Orleans
1985-86	Medical Consultant, Kimberly Services
1985-86	Locum Tenens, Michael Haydel, M.D., Gretna, La.
1986-88	Practice Associate of Richard Gugelmann, M.D., Cary, N.C.
1988-90	House Pediatrician, Washington Adventist Hospital, Tacoma Park, MD
1989-91	Physician, Capitol Area Permanente Medical Group, Kensington, MD
1990-98	Medical Officer, Division of Vaccine Injury Compensation, Bureau of Health Professions, HRSA, Rockville, MD
1997-	Clinical Instructor, Department of Pediatrics, Georgetown University
1998-	Deputy Chief, Genetic Services Branch, Maternal and Child Health Bureau, HRSA, Rockville, MD

PROFESSIONAL ORGANIZATIONS

Fellow, American Academy of Pediatrics
American Public Health Association

LICENSURE

1982	Louisiana (inactive)
1986	North Carolina (inactive)
1988	Maryland (through 09/30/05)

SPECIALTY CERTIFICATION

American Board of Pediatrics (March 1988)

PUBLIC HEALTH SERVICE ACTIVITIES (selected)

Project Officer, Institute of Medicine's Vaccine Safety Forum
Member, PHS Task Force on Safer Childhood Vaccines
DVIC Liaison, Scientific Subcommittee, Advisory Commission on Childhood Vaccines
BHPr representative, Secretary's Advisory Committee on Infant Mortality
Member, HRSA Human Subjects Committee

COMMUNITY ACTIVITIES (selected)

D.C. Coalition for Environmental Justice's Lead Poisoning Prevention Speakers Bureau
Chairperson, Board of Directors, Parents of Preschoolers, Inc.
Volunteer physician, Mobile Medical Care, 1993-94
Volunteer physician, Washington Free Clinic 1996-98

PAST RESEARCH ACTIVITIES (selected)

Human complement system
Hemoglobinopathies
Hemophilia A and HIV

AWARDS

March of Dimes Summer Science Research Grant for Medical Students
HRSA Administrator's Special Citation
Secretary's Award for Distinguished Service

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Desposito F, Lloyd-Puryear MA, Tonniges TF, Rhein F, Mann M. Survey of pediatrician practices in retrieving statewide authorized newborn screening results. Pediatrics 2001;108(2):E22.

Kaye CI, Laxova R, …Mann M, …. Integrating genetic services into public health – guidance for state and territorial programs from the National Newborn Screening and Genetics Resource Center (NNSGRC). Community Genet 2001;4:175-196.

Linzer DS, Lloyd-Puryear MA, Mann M, and Kogan MD. Evolution of a Child Health Profile Initiative. J Public Health Management Practice, 2004, Nov (Suppl), S16-S23.

CURRICULUM VITAE

BRADFORD L. THERRELL, JR.

ADDRESS

Director, National Newborn Screening and Genetics Resource Center
1912 West Anderson Lane Suite 210
Austin, Texas 78757

EDUCATION

B.S. 1966 - Chemistry - Mississippi College (Special Distinction, Honors)
M.S. 1969 - Inorganic Chemistry - The Florida State University
Ph.D. 1971 - Inorganic Chemistry -The Florida State University

CERTIFICATION

American Board of Bioanalysis - High-Complexity Clinical Laboratory Director

EXPERIENCE

1999 -	Professor, Department of Pediatrics, UTHSCSA, San Antonio, Texas
1999 -	Director, National Newborn Screening and Resource Center, Austin, Texas
1979 - 1999	Chemical Services Division Director, TDH Bureau of Laboratories, Austin, Texas
1974 - 1979	Clinical Chemistry Branch Supv, TDH Bureau of Laboratories, Austin
1971 - 1973	Project Director (Chemist) of Title XIX Laboratory Project

PROFESSIONAL ACCOMPLISHMENTS

1999-present	Director, U.S. Nat'l Newborn Screening and Genetics Resource Center
1997-present	Editorial Board - *JOURNAL OF MEDICAL SCREENING*
1997-present	Editorial Board - *GENETIC TESTING*
1996-1999	Chairperson - TEXGENE Newborn Screening Committee
1995-present	Expert Reviewer - International Atomic Energy Agency
1995-present	NCCLS Subcommittee on Newborn Screening
1995-1998	Secretary of Policy-Council of Regional Networks for Genetic Services
1993-1999	President - International Society for Neonatal Screening (ISNS)
1991-1995	Chairperson - Newborn Screening Committee, CORN
1991-1996	Co-Editor - *SCREENING* (Journal of the ISNS)
1987-present	U.S. Health and Human Services Select Panel on Neonatal Screening
1987-1999	Editor-in-Chief - *Infant Screening* (International Newsletter)
1987-1993	Secretary - International Society for Neonatal Screening (ISNS)

INTERNATIONAL ACTIVITIES

1982-present	Over 75 invited lectures presented in foreign countries
1987-present	Founding member, Secretary, and President of the ISNS
1988-present	Member of organizing committees for15 foreign screening meetings.

1991-present Faculty - Technology for Infantile and Neonatal Screening - Sapporo
1995-present Expert review activities for 15 foreign projects to improve infant health

PUBLICATIONS

BOOKS – Editor or co-editor of four books including:

Therrell BL Jr (ed) Laboratory Methods in Neonatal Screening. Washington, DC: American Public Health Association, 1993.

Therrell BL Jr (ed) Advances in Neonatal Screening. Amsterdam: Elsevier Science Publishers, 1987.

CHAPTERS – Author or co-author of five book chapters - Abbreviated titles:

Screening for congenital hypothyroidism, Automation and computerization, Laboratory methods for hypothyroidism, Hemoglobinopathy screening techniques for newborns, and Methods for phenylalanine analysis in newborns, Newborn Screening for CAH

MONOGRAPHS – Author or co-author of 6 monographs including 2 for the World Health Organization (*Guidelines for prevention and control of hypothyroidism*, and *Guidelines for prevention and control of phenylketonuria).*

ARTICLES – Author or co-author of over 115 scientific articles in the areas of: public health policy, computerization, automation, chemistry, microbiology, endocrinology, hematology, and newborn screening including:

Therrell BL Jr, Panny SR, et.al. U.S. Newborn screening system guidelines: statement of the Council of Regional Networks for Genetic Services. *Screening* 1992;1:135-147.

Therrell BL, Hannon WH, et.al. Guidelines for the retention, storage, and use of residual blood spot specimens after newborn screening analysis: Statement of the Council of Regional Networks for Genetic Services. *Biochem and Molec Med* 1996;57:116-124.

Meaney FJ, Kinney S, Therrell BL, et.al. Assessing genetic risks - implications for health and social policy: response from the Newborn Screening Committee of the Council of Regional networks for Genetic Services. *Screening* 1996;4:247-249.

Therrell BL, Berebaum SA, Manter-Kapanke V, et.al. Results of screening 1.9 million Texas newborns for 21-hydroxylase-deficient congenital adrenal hyperplasia. *Pediatrics* 1998;101:583-590.

Therrell BL. U.S. newborn screening policy dilemmas for the twenty-first century. Molec Genetics and Metab 2001 ; 74:64-74.

Larsson A and Therrell BL. Newborn screening: the role of the obstetrician. Clin Obstetr Gynecol 2002; 45:697-710.

Appendix 2 – Review Focus and Agenda

Focus of Review

(Submitted by the California Department of Health Services)

1. **Business Practice**
    a. Organization, administration and infrastructure of the California NBS program.
    b. Assessment of its capacity to handle >540,000 newborn blood samples to be screened for genetic conditions including metabolic disorders and its ability to screen for additional conditions as scientific data supports its value.
    c. Efficiency
    d. Past history, experience and ability
    e. Communication with specialists, primary care providers, and families of affected infants
    f. Documentation
    g. Educational materials for patients and provider

2. **Technical Review**
    a. Quality Control and Quality Assurance
    b. Reliability and reproducibility
    c. Diagnosis, management, follow-up and counseling
        i. Organizational and individual responsibilities for medical, laboratory, and follow-up
    d. Consolidation of newborn screening program

3. **Program Evaluation**
    e. Data collection and analysis
    f. Long term tracking and outcome evaluation
    g. Cost Benefit Analysis
        i. Comparing costs with costs avoided and other state program costs which include that of contracting with private organizations.

Other Considerations:

Comparison of California Newborn Screening Program with other states for areas of strength and improvement

Technical Assistance Review of the California Newborn Screening Program
Department of Health Services
850 Marina Bay Parkway
Richmond, CA 94804
February 24-25, 2005

AGENDA

Thursday, February 24

8:00-8:30am	**Entrance Discussion and Orientation** Room RLC F-174	**Les Newman**
	Conference call	**Catherine Camacho** **Beth Fife** **Dr. Susann Steinberg**
8:30-9:30am	**Program Overview** **Budget** Room RLC F-174	**Kathleen Velazquez** **Les Newman**
10:00-Noon	**Newborn and Prenatal Screening Laboratory** Kaiser Permanente, 1725 Eastshore Highway Berkeley, (510) 559-4720	**Dr. John Sherwin**
1:15-2:45pm	**Demonstration of IT Support (SIS)** Room RLC F-174	**Dea Harrell**
2:45-5:00pm	**Data Collection** **Clinical Services Follow-Up** **Lab Services and Tour Genetic Disease Lab** Richmond Laboratory Complex	**Dr. Fred Lorey** **Kathleen Velazquez** **Dr. John Sherwin**

Friday, February 25

9:00-11:00am	**NBS Program Area Service Center** Kaiser Permanente, 280 W. MacArthur Blvd Oakland, (510) 752-6192	**Kathleen Velazquez**
11:15-Noon	**Kaiser Hospital** Oakland	**Kathleen Velazquez**
1:30-3:00pm	**Meet with NBS program staff** RLC F-174	**Dr. George Cunningham** **GDB staff**
3:00-5:00pm	**Exit Interview** RLC F-174	**Catherine Camacho** **Beth Fife** **Les Newman**
	Conference Call	**Dr. Susann Steinberg**

Appendix 3 – Article

U. S. Newborn Screening System Guidelines: Statement of the Council of Regional Networks for Genetic Services (CORN).

Screening 1992;1:135-147.

Appendix 4 – Executive Summary

Serving the Family from Birth to the Medical Home:
N*ewborn Screening a Blueprint for the Future*

Pediatrics 2000;106(suppl 2):383-427.

Appendix 5 – Executive Summary

Newborn Screening:
Toward a Uniform Screening Panel and System

ftp://ftp.hrsa.gov/mchb/genetics/screeningdraftsummary.pdf

Appendix 6 – MS/MS Cost Studies

Newborn Screening by Tandem Mass Spectrometry for Medium-Chain Acyl-CoA Dehydrogenase Deficiency: A Cost Effectiveness Analysis. **Pediatrics August 2003;1005-1015.**

Cost Benefit Analysis of Universal Tandem Mass Spectrometry for Newborn Screening. **Pediatrics 2002;110:781-786.**

Appendix 7 – Article

Long-Term Developmental Outcomes of Children Identified Through a Newborn Screening Program with a Metabolic or Endocrine Disorder: A Population-Based Approach

The Journal of Pediatrics August 2003;236-242.

Appendix 8 - Article

Data Integration and Warehousing: Coordination Between Newborn Screening and Related Public Health Programs

Southeast Asian Journal of Tropical Medicine and Public Health 2003;34 Suppl 3:63-8.

Appendix 8 – Example Annual Report (Excerpts)

Nebraska Newborn Screening Program